

Comparison of the integrated pulmonary index with cardiac risk scores in acute coronary syndromes

Comparison of IPI with cardiac risk scores in ACS

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Abstract

Aim: In this study, we aimed to investigate the availability of the Integrated Pulmonary Index (IPI) score in predicting the risk of the major adverse cardiovascular event (MACE) in patients with acute coronary syndromes (ACS).

Material and Methods: This study was planned as a prospective single-centered study and the cardiac risk scores and IPI were calculated on the arrival of patients with ACS in the emergency department. The Thrombolysis in Myocardial Infarction (TIMI), history, ECG, age, risk factors, troponin (HEART), and global registry of acute cardiac events (GRACE) risk scores were compared with the obtained IPI score. The MACE was defined as death within the last month since its arrival; IPI's prediction rates of MACE risk were investigated.

Results: In the study, 381 patients were included and analyzed. MACE was detected in 105 (27.6%) patients. AUC values of TIMI, HEART, GRACE scores, and arrival high-sensitive cardiac troponin I in predicting MACE were 0.819, 0.737, 0.695 and 0.731, respectively, and statistically significant differences were found ($p < 0.001$). There were negative correlations and statistically significant differences with the IPI, TIMI, HEART, and GRACE scores ($p < 0.001$). The IPI score was found to predict MACE with 83.0% sensitivity and 74.3% specificity with >4 breakpoints (AUC=0.799).

Discussion: Our study is the first study in the literature in which IPI predicts risk factors in the ACS. The IPI has been found to predict cardiovascular events in accordance with cardiac risk scores at 30-day follow-up, and it is beneficial for emergency physicians to use IPI with other cardiac risk scores in the prediction of MACE in ACS.

Keywords

Coronary disease; Pulmonary index; Risk scores; Emergency department; Cardiovascular event

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Introduction

Acute coronary syndromes (ACS) constitute an important part of emergency department (ED) applications and deaths all over the world [1, 2]. Although ACS-related mortality and morbidities have decreased due to improvements in diagnosis and treatment; they are still seen at higher rates [3, 4]. ACS is an ischemic myocardial disease and includes ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). NSTEMI and UA have similar pathophysiology, and a likewise clinical approach is proposed. Therefore, NSTEMI and UA are referred to as non-ST elevation (NSTEMI) ACS [5].

Many parameters such as physical examination, history, clinical status, electrocardiography (ECG), biomarker, and risk scores are used for accurate and rapid diagnosis of ACS. According to diagnostic ECG changes, STEMI is quickly transferred to the coronary angiography unit and reperfusion is performed [6]. However, NSTEMI-ACS diagnosis is more complicated and difficult in terms of emergency physicians than STEMI. Therefore, NSTEMI-ACS patients pose an important problem for emergency services. The AHA/ACC guidelines suggested that a risk classification should be made based on the likelihood of ACS when deciding to hospitalize patients with suspected ACS. It was emphasized that among these risk classifications at class 1 recommendation level, thrombolysis in myocardial infarction (TIMI), history, ECG, age, risk factors, troponin (HEART) and global acute cardiac events logbook (GRACE) scores can be used [3]. These risk scores were developed to evaluate prognosis in ACS patients and to determine the major adverse cardiovascular events (MACE) risk in ACS [7].

Integrated Pulmonary Index (IPI) shows the respiratory status of patients objectively and simply by non-invasive method. By giving a real-time analysis of patients' end-tidal carbon dioxide (PetCO₂), respiratory rate, pulse, and peripheral oxygen saturation (SpO₂) gives the clinician a single value between 1 (immediate intervention required) and 10 (normal) [8]. IPI is used for the early detection of respiratory problems and monitoring of ventilation [9]. Using IPI, it can be determined whether patients need additional clinical evaluation and intervention [10]. It is seen that IPI is generally used to follow ventilation and oxygenation in processes that require sedation [8-10]. Within pathophysiological knowledge, cardiovascular and respiratory functions are known to be closely related. Pulmonary functions are also negatively affected by cardiovascular dysfunction [11, 12]

Therefore, respiratory functions may be affected in ACS, and IPI values may vary as well.

ACS is a common problem of the emergency department. Despite the presence of many cardiac risk scores and cardiac biomarkers, low-risk ACS remains uncertain for emergency services. Therefore, in this study, we aimed to compare cardiac risk scores with IPI in determining MACE risk in ACS patients.

Material and Methods

Study design and setting

This study is a prospective single-center clinical study examining the correlation between IPI by TIMI, HEART, and GRACE risk scores of patients diagnosed with ACS in predicting

serious events. This study was performed in the ED of a tertiary university hospital. This emergency service is a tertiary ED serving 120,000 patients annually. Approval was obtained from the local ethics committee for the study. Written consent was obtained from patients who agreed to participate in the study by giving detailed information to all patients.

Age, gender, blood pressure, pulse rate, respiratory rate, body temperature, oxygen saturation, TIMI, HEART and GRACE risk scores and IPI values of patients who agreed to participate in the study were recorded.

Patients

Patients who applied to the ED for 6 months due to chest pain were included in the study. These patients were evaluated for suitability for the study. Patients with suspected ACS, ≥ 18 years, and chest pain lasting more than 5 minutes were included in the study. Patients who did not agree to participate in the study, pregnant women, atypical chest pain due to other reasons, unstable and intubated patients, patients with chronic obstructive pulmonary disease and other lung pathology, patients with cognitive impairment, active psychiatric disease, and cancer patients were excluded from the study.

Test methods

The patients who applied to the ED due to chest pain were taken the ECG within the first 10 minutes and ACS was classified. The diagnosis of ACS was made according to the fourth universal definition of myocardial infarction [13]. Patients diagnosed with ACS were divided into two groups as STEMI and NSTEMI-ACS.

TIMI, HEART, and GRACE risk scores were calculated as indicated in the literature [16, 14, 15]. The parameters used in all three risk scores consist of the data obtained during the patients' application to the ED.

High-sensitive cardiac troponin I (hs-cTnI) and other biochemical tests levels of the patients included in the study were studied with a Unicel DXI 600 Access Immunoassay System (Beckman Coulter, Porterville, CA, USA) device by a chemical immunoassay method. If the level of troponin I studied from the blood sample taken in the application was below the threshold value (<11.6), 0 points were given. If troponin I level is between one and two times of the threshold value, 1 point is given, and if the threshold value is more than twice, 2 points are given.

IPI device (Capnostream-20, Medtronic, Israel) is a device that uses PetCO₂, respiratory rate, SpO₂ and pulse rate mathematically. It calculates the values of these four parameters simultaneously. At the end of this calculation, it gives a single value between 1 and 10. These values are as follows: 1-2: requires immediate intervention, 3-4: require intervention, 5-6: require attention and may require intervention, 7: close to normal range; requires attention, 8-9: within the normal range, 10: normal.

The IPI score was compared to TIMI, HEART, and GRACE risk scores and used to predict MACE in patients.

Patient follow-up

MACE has been defined as the occurrence of death from any cause (except trauma, cancer) within 30 days of patients' initial entry into the ED. The patients were followed up for 30 days and at the end of the 30th day; it was determined whether a death incident had occurred from the Ministry of Health's death reporting system. Accordingly, the patients were divided into

two groups (with or without MACE).

Analysis

SPSS version 25 (IBM Corp. in Armonk, NY) and MedCalc version 16 (MedCalc Software bvba, Ostend, Belgium) were used for statistical analysis. The Kolmogorov-Smirnov test was used for normal distribution. Descriptive statistics are given as frequency (n) and percentage (%) for categorical variables and median with interquartile range (IQR) for variables that do not show normal distribution. Group comparisons for variables without normal distribution were made by the Mann-Whitney U test. Spearman’s correlation analysis was used to investigate the relationship between variables that did not show normal distribution. ROC analysis was used to predict the accuracy of IPI, TIMI, HEART, and GRACE scores, and hs-cTnl value in predicting MACE in ACS. The area under the ROC curves (AUC) of the IPI, TIMI, HEART, and GRACE scores and the hs-cTnl value were calculated. The Youden J index was used to estimate the best cut-off points. Sensitivity and specificity were calculated with a 95% confidence interval (CI). In the study, p<0.05 was considered significant.

Results

Patients

During the study period, 1,231 patients applied to the ED due to chest pain. Within the scope of our study, a total of 393 patients who met the exclusion and inclusion criteria and signed informed consent forms were included in the study. While MACE monitoring of patients was performed, 12 patients were excluded from the study due to missing data in the first month. The remaining 381 patients were analyzed (Figure 1). ACS patients were divided into two groups as STEMI and NSTEMI-ACS and their mean age was 62.98 ±15.5 years and 55.21±15.76 years, respectively. When the cardiac risk scores and IPI score of the patients were compared, it was found that the TIMI, HEART, and GRACE scores were higher in the STEMI group and the IPI score was lower in the STEMI group. Likewise, the hs-cTnl value measured during admission was found high in the STEMI group. Patients in the STEMI group constitute 88.6% (n = 93) of the deaths in the first month after the patients’ application to the ED. The demographic and clinical features of the patients are given in Table 1.

The MACE ratios for the cardiac risk scores and IPI score of the patients are shown in Table 2. Among all four scores, a high rate of MACE was observed in high-risk patients (59.0%, 79.0%, 49.5%, and 65.3%, respectively). According to the HEART score, 3.1%, 46.2% and 93.7% MACE were observed in patients in low, medium, and high-risk groups, respectively. In the GRACE score, MACE was observed at a higher rate (35.2%) than the other three scores in the low-risk group. Similar to the other three cardiac risk scores, the IPI score was found to have high rates of MACE in the high-risk group. Also, all three cardiac risk scores, IPI score and hs-cTnl value were statistically significant in predicting MACE (p <0.001).

Test results

The correlation between cardiac risk scores and the IPI score of ACS patients were analyzed. The IPI score was found to be negatively correlated with the TIMI, HEART, and GRACE risk scores and hs-cTnl value (r=-0.447; -0.467; -0.542 and

Table 1. Demographics and clinical characteristics of the patients with ACS

	STEMI (n=129)	NSTEMI-ACS (n=252)
Age (Years)	62.98 ± 15.5 (22-87)	55.21 ± 15.76 (19-95)
Sex, n (%)		
Female	71 (55)	115 (45.6)
Male	58 (45)	137 (54.4)
Total	129 (100)	252 (100)
Chronic Diseases, n (%)		
No	38 (29.5)	119 (47.2)
HT	34 (26.4)	35 (13.9)
DM	1 (0.8)	16 (6.3)
CAD	18 (14)	21 (8.3)
CRF	-	2 (0.8)
DM + HT	26 (20.2)	18 (7.1)
DM + CAD	-	11 (4.4)
HT + CAD	5 (3.9)	11 (4.4)
CAD + DM + HT	7 (5.4)	12 (4.8)
DM+HT+CRF	-	1 (0.8)
Other	-	6 (2.4)
Total	129 (100)	252 (100)
Family history, Positive, n (%)	64 (49.6)	70 (27.8)
Smoking, Positive, n (%)	71 (55)	95 (37.7)
History of Aspirin use in the last 7 days, n (%)	67 (51.9)	96 (38.1)
Arrival examination, Median (IQR)		
Systolic blood pressure (mmHg)	114 (96-140)	130 (116-147.75)
Diastolic blood pressure (mmHg)	75 (64-90)	77 (70-88)
Heart rate (BPM)	75(60-96)	80 (72.25-91)
Body temperature (°C)	36.4 (36.4-36.6)	36.5 (36.4-36.7)
Respiratory rate (BrPM)	23 (18-33)	19 (17-21)
Oxygen saturation level (%)	90 (80-95)	94 (92-96)
Arrival examination, Median (IQR)		
TIMI Score	5 (3-6)	2 (1-3)
HEART Score	8 (7-9)	5 (1-7)
GRACE Score	129 (59-153)	72.5 (52-103.75)
IPI Score	3 (2-6)	8 (6-9)
Arrival examination, Median (IQR)		
High-sensitivity troponin-I, ng/L	216 (56-1564.5)	11.15 (1.53-205.25)
Creatinine, mg/dL	0.90 (0.80-1.40)	0.83 (0.71-0.99)
Low-density lipoprotein, mg/dL	156 (129-178)	123.5 (96.5-142)
High-density lipoprotein, mg/dL	37 (30-40)	39 (35-45)
Triglyceride, mg/dL	168 (137-211)	139 (103-187)
Cholesterol, mg/dL	200 (180-231)	182 (134-211)
Death in the past month, n (%)	93 (88.6)	12 (11.4)

Note: HT: Hypertension, DM: Diabetes mellitus type 2, CAD: Coronary artery disease, CRF: Chronic renal failure, BPM: Beats per minute, BrPM: breaths per minute, IPI: Integrated Pulmonary Index, TIMI: Thrombolysis in Myocardial Infarction, HEART: History, ECG, Age, Risk Factors, Troponin, GRACE: Global Acute Cardiac Events Registry

-0.179, respectively). All these correlations were statistically significant at the level of p <0.001.

In the estimation of MACE in patients diagnosed with ACS and comparing the patients with the cardiac scores and the first hs-cTnl value measured with the IPI score are given in Table 3. The IPI score was found to predict MACE with 83.0% sensitivity and 74.3% specificity with >4 breakpoints (AUC = 0.799). The ROC curve of ACS patients is shown in Figures 2a and 2b. AUC values

of TIMI, HEART, GRACE scores, and arrival hs-cTnI in predicting MACE were 0.819, 0.737, 0.695, and 0.731, respectively. These scores and hs-cTnI value used to predict MACE were statistically significant.

Discussion

According to our research of the literature, this study is the first to investigate the applicability of the IPI score to predict MACE in ACS patients and to guide the decisions the of the ED physicians to discharge patients. In this study, the compatibility between IPI score and TIMI, HEART, and GRACE scores, and hs-cTnI value in predicting MACE in ACS patients was evaluated. For this purpose, the correlation between IPI score and TIMI, HEART, and GRACE scores and hs-cTnI value after the diagnosis of ACS according to the fourth universal definition of myocardial infarction [13] in patients admitted to the ED due to chest pain

was examined. A statistically negative correlation was found between IPI and these values. In predicting MACE in ACS, the ROC curve showed a high degree of similarity between the IPI score and the TIMI, HEART, and GRACE scores and hs-cTnI value in comparison of the AUC curve. For the best cut-off points, the sensitivity of the IPI score was 83.0%, the specificity was 74.3%, and it had sensitivity and specificity similar to other cardiac risk scores and hs-cTnI. In addition, we found that IPI has an accuracy equivalent to other cardiac risk scores and hs-cTnI value in predicting MACE in ACS patients.

Considering the studies in the literature, the IPI score has been used to monitor patients' respiratory functions in sedation practices and intensive care [8-10, 16, 17]. In these studies, it was stated that IPI detected the hypoxia event that occurred in the patient during the follow-up and after the procedures with high sensitivity and specificity [10, 16]. As understood from the studies in the literature, IPI has been found to easily detect respiratory pathologies in a simple, correct and clear manner. Therefore, it has been determined that it can play a key role in monitoring respiratory functions and intervening immediately.

This study was carried out based on the results of the studies in the literature that cardiovascular pathologies affect the respiratory system and are closely related [18-20]. Our study is the first study in the literature in this sense, and it has been determined that IPI predicts risk factors in the cardiovascular system. In our study, it was found that IPI is similar to the cardiac risk scores and hs-cTnI value in predicting MACE in ACS. The higher the score in cardiac risk scores and hs-cTnI, the greater the risk of MACE being seen, while the lower the score in IPI score, the greater the risk of MACE being seen. It was also observed that there was a negative correlation between IPI score and other studied risk scores and hs-cTnI and it was statistically significant (p <0.001).

Cardiac risk scores have an important place in the diagnosis, exclusion, discharge and prediction of MACE in ACS. However, as understood from the studies in the literature, there is no appropriate gold standard risk score [6, 14, 15, 21, 22]. However, when evaluating these patients, scoring should still be done in accordance with the ACS guidelines. All three of the cardiac risk scores, TIMI, HEART and GRACE risk scores, are used in cardiac risk classification and forecasting MACE. American College of Emergency Physicians (ACEP) recommends using the HEART score as a B level recommendation and TIMI score as a C level recommendation to estimate the 30-day MACE rate in potential NSTEMI patients. Thus, it was emphasized that the duration of

Table 2. The occurrence of MACE (death in the past month) according to risk groups

	Patients (n)	MACE (n)	MACE (%)	p- value
TIMI Score				
Low (1-2)	114	2	1.9	<0.001
Intermediate (3-4)	131	41	39.0	
High (5-7)	136	62	59.0	
HEART Score				
Low (0 - 3)	70	5	4.8	<0.001
Intermediate (4-6)	130	17	16.2	
High (7-10)	181	83	79.0	
GRACE Score				
Low (< 88)	246	37	35.2	<0.001
Intermediate (89-118)	71	16	15.2	
High (> 118)	64	52	49.5	
IPI Score				
Normal (10)	38	4	10.5	<0.001
Within normal range (8-9)	133	12	9.0	
Close to normal range; requires attention (7)	25	4	16.0	
Requires attention and may require intervention (5-6)	60	7	11.7	
Requires intervention (3-4)	76	46	60.5	
Requires immediate intervention (1-2)	49	32	65.3	
Hs-cTnI	381	105	27.63	<0.001

Note: TIMI: Thrombolysis in Myocardial Infarction, HEART: History, ECG, Age, Risk Factors, Troponin, GRACE: Global Acute Cardiac Events Registry, IPI: Integrated Pulmonary Index, Hs-cTnI: High-sensitivity troponin I.

Table 3. Comparison of AUC of the ROC curves of IPI, TIMI, HEART, GRACE scores and hs-cTnI data of ACS patients.

	IPI Score	TIMI Score	HEART Score	GRACE Score	hs-cTnI	p- value
AUC (95% CI)	0.799 (0.746-0.852)	0.819 (0.777- 0.857)	0.737 (0.689-0.780)	0.695 (0.646-0.741)	0.731 (0.683-0.775)	<0.001
Youden index (95% CI)	0.087	0.4625	0.3960	0.4937	0.3989	
Associated criterion	>4	≤2	>6	>115	>17	
Sensitivity, % (95% CI)	83.0 (82.61-83.34)	75.24 (65.9-83.1)	76.19 (66.9-84.0)	68.57 (58.8-77.3)	89.52 (82.0-94.7)	
Specificity, % (95% CI)	74.3 (73.9-74.7)	71.01 (65.3-76.3)	63.41 (57.4-69.1)	80.80 (75.6-85.3)	50.36 (44.3-56.4)	

Note: TIMI: Thrombolysis in Myocardial Infarction, HEART: History, ECG, Age, Risk Factors, Troponin, GRACE: Global Acute Cardiac Events Registry, IPI: Integrated Pulmonary Index, hs-cTnI: High-sensitivity troponin I, AUC: area under curve.

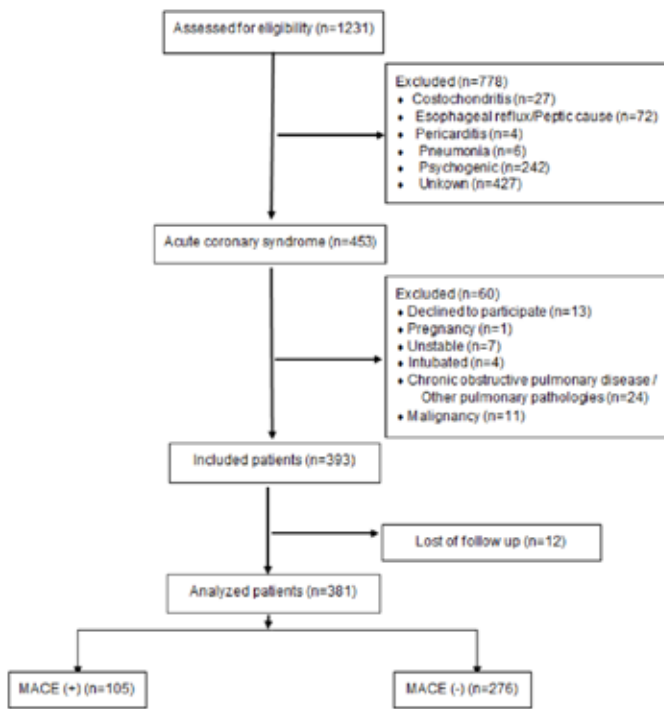


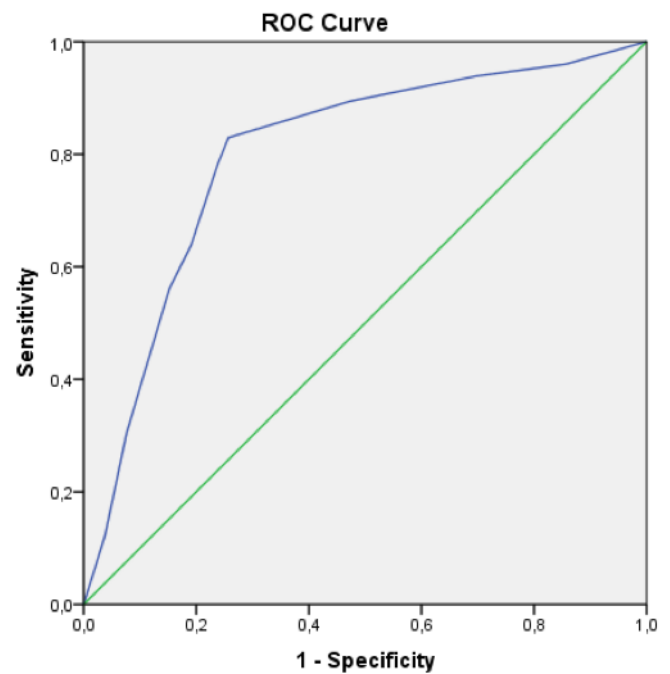
Figure 1. Flow-chart of patients in the study

the stay in the ED of low-risk patients would be reduced [6]. Than M et al. emphasized that patients admitted to the ED with chest pain can easily be discharged if their TIMI risk score is zero in patients with normal ECG, normal O, and 2nd-hour hs-cTnI [19]. It was also stated that the risk of MACE in these patients is very low, and therefore, it has been determined that patients with chest pain can be discharged early from the ED and the observation periods are shortened. In our study, the sensitivity of the TIMI score was 75.24% and specificity was 71.01%, and the TIMI score estimation of MACE was statistically significant ($p < 0.001$). Furthermore, in our study, it was found that the IPI score was more sensitive and specific in predicting MACE than the TIMI score.

Huis in't Veld MA et al. investigated that the ROC curve AUC areas of TIMI, HEART, and GRACE were 0.75, 0.83, and 0.70, respectively and statistically significant ($p < 0.0001$) [14]. In our study, these risk scores were 0.82, 0.74, and 0.70, respectively ($p < 0.001$). Compared with their study, in our study, the TIMI score predicted higher MACE risk, while the HEART score predicted a lower MACE risk.

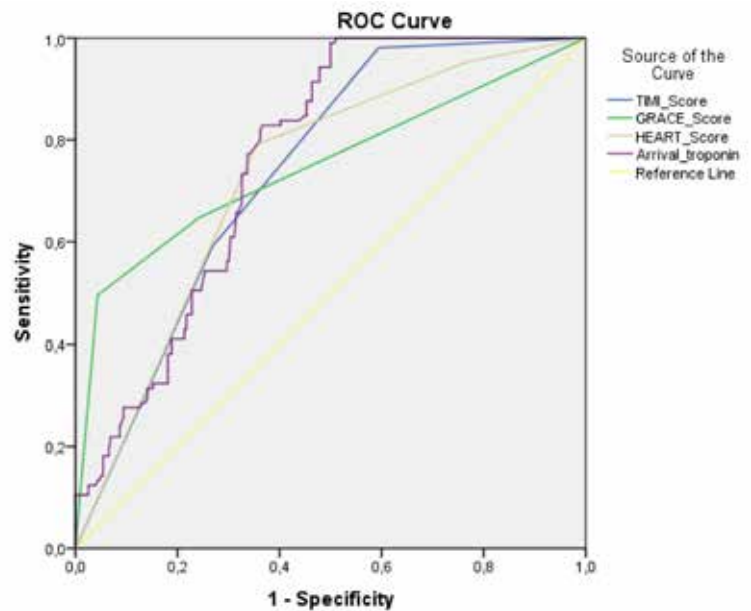
In a study by Tomaszewski CA et al., it was stated that most data related to risk scores were related to TIMI and HEART scores. It was emphasized that both scores can predict MACE at high rates and can be used to predict MACE in ACS [6]. Due to these predictions of cardiac risk scores, it has an important place in the management of patients with chest pain in emergency departments. In addition to these risk scores, MACE becomes better predictable when evaluating ACS together with hs-cTnI. Various cardiovascular risk scores are used in emergency departments to complete the clinical evaluation and predict MACE. The use of the IPI score in addition to these risk scores and hs-cTnI will further increase the clinical assessment and the MACE prediction rates.

In the multinational and prospective GRACE study conducted



Diagonal segments are produced by ties.

Figure 2a. ROC curves of IPI data of ACS patients



Diagonal segments are produced by ties.

Figure 2b. Comparison of ROC curves of TIMI, HERAT, GRACE scores, and High-sensitivity troponin I data of ACS patients

by Fox KAA et al., it was stated that biomarkers and ECG would not be sufficient to evaluate cardiovascular risk in ACS patients [23]. It was emphasized that common clinical variables that provide more accurate prognostic information and guide treatment should be used for this. As a result, they stated that the GRACE risk score is a fast and widely used method to evaluate MACE in patients with ACS and can guide the patient triage and treatment. In our study, it was found that the GRACE risk score predicted MACE with 68.57% sensitivity and 80.80% specificity. The IPI score, on the other hand, was found to be more sensitive but less specific in predicting MACE than the GRACE score.

Limitations

Our study is the first to investigate the applicability of the IPI score to predict MACE in ACS patients and to guide the decisions of the ED physicians to discharge. However, our study also have some limitations. Firstly, our study was a single-center study and the sample size was relatively small. Secondly, the sensitivity and specificity of the cardiac risk scores in our study to predict MACE were lower than in some studies in the literature. This is due to the fact that in our study we took MACE as a death that occurred only in the first month, unlike the studies in the literature. Further multicentre with larger sample size studies with wider MACE criteria are required.

Conclusion

In conclusion, our study is the first study in the literature investigating the clinical use of IPI score in predicting MACE in ACS. In the literature, it is seen that many cardiac risk scores are used to predict MACE in ACS, and the gold standard has not been determined yet. Our study found that the IPI score is compatible with TIMI, HEART, and GRACE risk scores and hs-cTnI in predicting MACE in ACS. Furthermore, the use of IPI score with these risk scores and hs-cTnI may better predict MACE in ED. Since our study is the first in the literature, more clinical studies are needed in order for the IPI score to be accepted as a guide for emergency physicians in ACS.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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